Open-label experience in Osteoarthritis and Rheumatoid Arthritis:

Study N49-96-02-024 is an ongoing, long-term open-label safety study of patients who previously participated in one of following nine phase II or III double-blind controlled studies:

- **N49-96-02-012 (RA)**
- **N49-96-02-013 (OA)**
- **N49-96-02-020 (OA)**
- **N49-96-02-021 (OA)**
- **N49-96-02-022 (RA)**
- **N49-96-02-023 (RA)**
- **N49-96-02-054 (OA)**
- **N49-97-02-062 (OA/RA)**
- **N49-97-02-071 (OA/RA)**

All patients treated in the long-term open label study previously participated in one of nine controlled studies. A 14-day rule was used to determine direct transfer status as follows:

- **If a patient received any celecoxib dose in the controlled study and transferred into the open label study within 14 days, the patient was considered a direct transfer patient and all previous study data were included in the long-term analysis (Day 1 of celecoxib is the first day of the double-blind study);**
- **If a celecoxib patient transferred after 14 days then Day 1 of celecoxib is the first day of the open label study**
- **Patients who received placebo or an active control agent in the double-blind study are evaluated as Day 1 of celecoxib in the open-label study regardless of the gap between studies.**

This multicenter study is/was designed to determine the long-term (up to two years) safety, including an evaluation of the incidence of any clinically significant gastrointestinal events, of Cx administered to patients with osteoarthritis OA or RA. Efficacy assessments (see below) are also being performed. The data cutoff date for the interim data listings included in this NDA is November 21, 1997. The results of the completed trial are pending at this time; it is anticipated to be completed in 12/99.

For two-year patients, visits included the Baseline, at Weeks 2 and 6, and at Months 3, 6, 9, 12, 15, 18, 21, and 24. For patients enrolled for one year, the Month 12 visit is the final study visit. For both two-year and one-year patients, study visits are to include review of any treatment-emergent signs and symptoms experienced since the previous visit. Safety assessments are generally combined for OA and RA.

Measures of arthritis efficacy include:

- **Patient's Assessment of Arthritis Pain on the Visual Analog Scale (VAS);**
- **Patient's Global Assessment of Arthritis;**
- **Physician's Global Assessment of Arthritis**
- **Functional Capacity Classification.**

These assessments will be performed on all patients at every visit, with the exception of the Patient's Assessment of Arthritis Pain on the Visual Analogue Scale (VAS), with the exception of patients previously enrolled in N49-97-02-062 or N49-97-02-071. Patients will undergo a physical examination at the Baseline visit and every six months thereafter. Clinical laboratory tests will be performed at every study visit. Two-year patients will complete a quality of life assessment (SF-36 Health Survey) at Baseline and every six months thereafter, and a Health Resource Utilization Questionnaire at every visit except Baseline. One-year patients will not complete the SF-36 Health Survey or the Health Resource Utilization Questionnaire at any study visit.

A radiologic examination (i.e., hand and wrist x-rays for patients with RA and either the Index knee or the Index hip for patients with OA) will also be performed at Baseline and the Month 12, or Early Termination, visit for all patients, except those previously enrolled in N49-97-02-062 or N49-97-02-071.

As of the cutoff date, a total of 4499 patients had entered the long-term, open-label safety study. A total of 3256 patients were still active in the study at the cutoff date; the remaining 1243 had prematurely terminated from the study. The longest duration of treatment (patient 0150001) was 522 days.

The table below briefly summarizes the disposition of patients to this point for study 024:

Table 7: Disposition of Patients in Protocol 024

Category	Placebo	Cx (all doses)	NSAIDs	Total
Pts able to enroll	1270	4422	2073	7765
Pts enrolled (%)	860 (68)	2776 (63)	863 (42)	4499 (58)
Pts at 12 months	-	-	-	3256 (72)

Reviewer's comment: There is a discrepancy between the number of patients still active and those that have terminated between this text (i.e. 3256 and 1243, respectively) and tables cited below of 61 patients. In other words, the tables suggest there are 61 patients still receiving Cx that the text states have been terminated from study 024.

In study 024, the doses of Cx allowed have ranged from 100-200 mg BID for OA and 200-400 mg BID for RA. This range was allowed to control symptoms (increased) or for tolerability reasons (reduced). As can be seen (***Appendix, Table A.45***), approximately 70 % of patients with either OA or RA, increased their dose beyond what is felt to be the therapeutic dose during the randomized controlled studies presented in this NDA (i.e. 100 mg BID for OA, 200 mg BID for RA). Of those that did increase their dose, most moved to a dose twice as high (i.e. 200 mg BID for OA, 400 mg BID for RA).

Of the efficacy parameters assessed in protocol 024, the Patient's Global Assessment of Arthritic Condition for OA and RA are presented (see ***Appendix, Figure A.1***); results are very similar for the Patient Assessment of Pain (VAS) and the Physician's Global Assessment for both the patients with OA and RA. Regarding figure 7 (OA) and figure 10 (RA) of Appendix figure A.1, it is noted by the sponsor:

"Although approximately 70% of OA patients did escalate the dose, there was no worsening of arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This data lends further support to the conclusion that celecoxib 100 mg BID is an efficacious dose and an increase to 200 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of OA."

"Although approximately 75% of RA patients did escalate their dose (to 300 or 400 mg BID), there was no evidence of worsening arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This finding lends further support to the conclusion that celecoxib 100 mg BID and 200 mg are efficacious doses and 400 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of RA".

Reviewer's comment: It could just as easily be argued that an escalation of the dose was required to maintain any long-term efficacy of Cx in OA and RA.

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Appendix Tables/Figures

Table A.1 Schedule of Observations and Procedures (Protocol 020)

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±2 days	Week 12 Day 84 ±2 days	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X				X	X
Clinical Lab Tests (a)	X		X	X(b)	X	X
QOL Assessment (c)		X	X		X	X
OA Assessments	X(d)	X	X	X	X	X
Discontinue NSAID or analgesic (e)	X					
Meet Flare Criteria		X				
Signs and Symptoms		X	X	X	X	X
APS Pain Measure (f)		X				
Patient Assessment of Function (f)		X				
Blood Samples for Plasma PK Levels (g)			X			
Dispense Study Medication		X	X	X		
Return & Count Study Med			X	X	X	X
Dispense Concurrent Medications Diary Card		X	X	X		
Retrieve Concurrent Medications Diary Card			X	X	X	X

a) Clinical laboratory tests included: **Hematology** (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; **Biochemistry** (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]); and **Urinalysis** (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). Serum pregnancy test for women of childbearing potential at Screening visit only.

b) PT and PTT tests were not performed at the Week 6 Visit.

c) SF-36 Health Survey.

d) Screening Arthritis Assessment data were collected by Searle but not entered in the database.

e) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.

f) American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. Patients enrolled in study prior to 8 August 1996 who already began taking study medication were not required to complete questionnaires.

g) Three blood draws were to be taken from 200 patients (approximately 40 per treatment group) at selected sites between Day 7 and 28 after first dose for determination of SC-58635 plasma levels.

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Table A.2 Baseline demographics (study 020, 021, 054-pooled)

12-Week Pivotal Studies 020, 021, and 054)

Baseline Characteristic	Placebo (n=664 [a])	Celecoxib 50 mg BID (n=671)	Celecoxib 100 mg BID (n=644 [a])	Celecoxib 200 mg BID (n=648)	Naproxen 500 mg BID (n=631)
Baseline Demographic Characteristics					
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	(b)(4)				
<65 years - N (%)	361 (54%)	378 (56%)	358 (56%)	353 (54%)	334 (53%)
≥65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin					
Asian - N (%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Caucasian - N (%)	577 (87%)	574 (86%)	569 (88%)	555 (86%)	553 (88%)
Hispanic - N (%)	22 (3%)	13 (2%)	7 (1%)	18 (3%)	11 (2%)
Other - N (%)	4 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Male - N (%)	198 (30%)	227 (34%)	203 (32%)	197 (30%)	201 (32%)
Baseline Index Joint and Disease Duration					
Baseline Index Joint					
Knee - N (%)	446 (67%)	455 (68%)	437 (68%)	435 (67%)	424 (67%)
Hip - N(%)	218 (33%)	216 (32%)	207 (32%)	213 (33%)	207 (33%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range	(b)(4)				
<5 years - N (%)	257 (39%)	281 (42%)	255 (40%)	273 (42%)	264 (42%)
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

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Table A.3 Baseline demographics (protocol 060, 087-pooled)

Week Pivotal Studies 060 and 087)

Baseline Characteristic	Placebo (n=476)[a]	Celecoxib 100 mg BID (n=474)	Celecoxib 200 mg QD (n=454)
Baseline Demographic Characteristics			
Age (years)			
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62.0 (11.59)
Range	(b)(4)		
<65 years - N (%)	260 (55%)	254 (54%)	257 (57%)
≥65 years - N (%)	215 (45%)	220 (46%)	197 (43%)
Race/Ethnic Origin			
Caucasian - N (%)	418 (88%)	408 (86%)	392 (86%)
Black - N (%)	42 (9%)	50 (11%)	41 (9%)
Hispanic - N (%)	7 (1%)	9 (2%)	6 (1%)
Asian - N (%)	1 (<1%)	0 (0%)	1 (<1%)
Other - N (%)	7 (1%)	6 (1%)	14 (3%)
Gender			
Female - N (%)	333 (70%)	321 (68%)	306 (67%)
Male - N (%)	143 (30%)	153 (32%)	148 (33%)
Disease Duration - Years			
Mean (Std. Dev.)	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)
Range	(b)(4)		
<5 years - N (%)	172 (36%)	158 (33%)	149 (33%)
≥5 years - N (%)	304 (64%)	316 (67%)	305 (67%)

Table A.4 WOMAC Index

How much pain do you have?

- walking on a flat surface
- going up or down stairs
- at night while in bed
- sitting or lying
- standing upright

Amount of joint stiffness

- How severe is your stiffness after first awakening in the morning?
- How severe is your stiffness after sitting, lying, or resting later in the day?

Ability to move around and to look after yourself - degree of difficulty

- descending stairs
- ascending stairs
- rising from sitting
- standing
- bending to floor
- walking on flat surface
- getting in/out of car
- going shopping
- putting on socks/stockings
- rising from bed
- taking off socks/stockings
- lying in bed
- getting in/out of bath
- sitting
- getting on/off toilet
- heavy domestic duties
- light domestic duties

Score: none, mild, moderate, severe, extreme

Table A.5: Osteoarthritis Severity Index (knee)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles, about 15 minutes)	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you go up a standard flight of stairs?	0 to 2
- Can you go down a standard flight of stairs?	0 to 2
- Can you squat completely?	0 to 2
- Can you walk on uneven ground?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.6: Osteoarthritis Severity Index (hip)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles, about 15 minutes)	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you put on socks by bending forward?	0 to 2
- Can you pick up an object from the floor?	0 to 2
- Can you go up a standard flight of stairs?	0 to 2
- Can you get into and out of a car?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.7.1 Physician's Global Assessment (Protocol 054)

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT).

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	213	207
MEAN	3.8	3.8	3.8	3.8	3.8
STD DEV	0.60	0.60	0.56	0.61	0.60
WEEK 2					
N	217	216	207	213	207
MEAN	3.3	3.0	2.7	2.5	2.5
STD DEV	0.90	0.83	0.82	0.85	0.85
WEEK 6					
N	217	216	207	213	207
MEAN	3.3	2.8	2.7	2.7	2.7
STD DEV	0.91	0.94	0.93	0.98	0.98
WEEK 12					
N	217	216	207	213	207
MEAN	3.2	2.9	2.9	2.9	2.9
STD DEV	0.90	0.94	0.95	1.02	1.02

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor)

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (N) (a)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	LINEAR TREND p-VALUE (d)
WEEK 2						<0.001
IMPROVED (b)	37(17%)	55(25%)	60(29%)	69(32%)	63(30%)	
NO CHANGE	172(79%)	158(73%)	145(70%)	140(66%)	141(68%)	
WORSENED (c)	8(4%)	3(1%)	2(<1%)	4(2%)	3(1%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	
WEEK 6						<0.001
IMPROVED (b)	42(19%)	68(31%)	70(34%)	80(38%)	63(30%)	
NO CHANGE	166(76%)	144(67%)	135(65%)	128(60%)	139(67%)	
WORSENED (c)	9(4%)	4(2%)	2(<1%)	5(2%)	5(2%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	
WEEK 12						0.001
IMPROVED (b)	50(23%)	59(27%)	66(32%)	63(30%)	66(32%)	
NO CHANGE	160(74%)	152(70%)	139(67%)	145(68%)	135(65%)	
WORSENED (c)	7(3%)	5(2%)	2(<1%)	5(2%)	6(3%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	

p-VALUES FOR TREATMENT COMPARISONS (d) :

	PLACEBO VS.	50MG BID VS.	100MG BID VS.	200MG BID VS.	NAPROXEN VS.	PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	0.001*	<0.001*	0.005	0.044*	0.158	0.261	<0.001*	0.042	0.626	0.709
WEEK 6:	<0.001*	<0.001*	<0.001	0.502	0.307	0.343	0.003	0.535	0.167	0.182
WEEK 12:	<0.001*	0.008*	0.004	0.038	0.011	0.493	<0.001*	0.010	0.015	0.015

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 2 to 1
(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-4; it is counted in grade type 4 or 5
(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation / Row Mean Scores Differ)
(e) Cochran-Mantel-Haenszel test of treatment correlation stratified by center (Row Mean Scores Differ)
* Statistically significant according to the hierarchy, testing sure primary pairwise comparisons only

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Table A.7.2 Physician's Global Assessment-continued (Protocol 054)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=117)	SC-58635 50MG BID (N=121)	SC-58635 100MG BID (N=120)	SC-58635 200 MG BID (N=117)	NAPROXEN 500MG BID (N=120)	OVERALL p-VALUE(a,	LINEAR TREND p-VALUE(b)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	1.6	1.9	2.1	2.2	2.2		
STD DEV	0.74	0.69	0.68	0.67	0.67		
LS MEAN CHANGE (c)	-1.5	-1.8	-1.9	-2.0	-2.0		
WEEK 6						<0.001	<0.001
OBSERVED MEAN CHANGE	1.8	2.0	2.2	2.2	2.2		
STD DEV	0.82	0.71	0.71	0.78	0.86		
LS MEAN CHANGE (c)	1.6	1.8	2.0	2.0	2.0		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	1.9	1.8	2.0	2.0	1.9		
STD DEV	0.88	1.04	0.91	1.03	1.06		
LS MEAN CHANGE (c)	1.8	1.7	1.9	1.9	1.8		

RATIO WITH 95% CONFIDENCE INTERVALS (e): 50MG BID VS. NAPROXEN; 100MG BID VS. NAPROXEN; 200MG BID VS. NAPROXEN

WEEK 2:	0.83 (0.71 to 0.97)	0.90 (0.78 to 1.04)	0.97 (0.84 to 1.12)
WEEK 6:	0.89 (0.74 to 1.07)	0.98 (0.82 to 1.18)	1.05 (0.89 to 1.24)
WEEK 12:	0.91 (0.76 to 1.08)	0.97 (0.81 to 1.16)	0.99 (0.83 to 1.18)

(a) VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY			SECONDARY						
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.031	0.155	0.845	<0.001	0.019	0.850	0.671
WEEK 6:	<0.001*	<0.001*	<0.001	0.397	0.449	0.577	<0.001	0.925	0.981	0.565
WEEK 12:	<0.001*	<0.001*	<0.001	0.601	0.769	0.427	<0.001	0.298	0.719	0.245

(a) This table is based on the last observation carried forward approach.
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.796 for week 2, 0.897 for week 6, and 0.916 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) 'RATIO' is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

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Table A.8.1 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)*

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	213	207
MEAN	3.8	3.8	3.9	4.0	3.9
STD DEV	0.61	0.64	0.61	0.59	0.64
WEEK 2					
N	217	216	207	213	207
MEAN	3.3	2.9	2.7	2.8	2.7
STD DEV	0.90	0.86	0.85	0.90	0.86
WEEK 6					
N	217	216	207	213	207
MEAN	3.3	2.9	2.8	2.8	2.8
STD DEV	0.97	0.97	0.95	1.08	1.01
WEEK 12					
N	217	216	207	213	207
MEAN	3.4	2.9	2.8	3.0	2.8
STD DEV	0.96	1.01	1.02	1.09	1.06

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor)
* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (%) (a)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	LINEAR TREND p-VALUE (d)
WEEK 2						<0.001
IMPROVED (b)	35(16%)	51(24%)	67(32%)	75(35%)	66(32%)	
NO CHANGE	171(79%)	160(74%)	137(66%)	132(62%)	138(67%)	
WORSENED (c)	11(5%)	5(2%)	3(1%)	6(3%)	3(1%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	
WEEK 6						<0.001
IMPROVED (b)	38(18%)	67(31%)	71(34%)	78(37%)	63(30%)	
NO CHANGE	162(75%)	145(66%)	131(63%)	126(59%)	139(67%)	
WORSENED (c)	17(8%)	6(3%)	5(2%)	9(4%)	5(2%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	
WEEK 12						0.001
IMPROVED (b)	36(17%)	56(26%)	65(31%)	61(29%)	70(34%)	
NO CHANGE	164(76%)	153(71%)	137(66%)	142(67%)	131(63%)	
WORSENED (c)	17(8%)	7(3%)	5(2%)	10(5%)	6(3%)	
TOTAL	217(100%)	216(100%)	207(100%)	213(100%)	207(100%)	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY		SECONDARY							
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	0.016	0.044	0.017	0.427	<0.001	0.072	0.954	0.784
WEEK 6:	<0.001*	<0.001*	<0.001	0.543	0.423	0.402	<0.001	0.837	0.464	0.266
WEEK 12:	<0.001*	0.007*	0.004	0.258	0.794	0.606	<0.001	0.151	0.677	0.174

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 2 to 1
(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5
(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation). Naproxen group was excluded
(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

BEST POSSIBLE

Table A.8.2 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL P-VALUE(c)	LINEAR TREND P-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.2	-1.1	-1.2		
STD DEV	0.96	0.92	0.90	0.96	0.90		
LS MEAN CHANGE (c)	-0.6	-0.9	-1.2	-1.1	-1.2		
WEEK 6						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.5	-0.9	-1.1	-1.1	-1.1		
STD DEV	1.09	1.02	1.05	1.04	0.99		
LS MEAN CHANGE (c)	-0.6	-1.0	-1.1	-1.1	-1.1		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.5	-0.8	-1.1	-1.0	-1.1		
STD DEV	1.06	1.06	1.06	1.07	1.07		
LS MEAN CHANGE (c)	-0.5	-0.9	-1.1	-0.9	-1.1		

Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):	50MG BID VS. NAPROXEN	100MG BID VS. NAPROXEN	200MG BID VS. NAPROXEN
WEEK 2:	0.78 (0.66 to 0.91)	0.97 (0.85 to 1.12)	0.93 (0.80 to 1.07)
WEEK 6:	0.92 (0.77 to 1.10)	1.01 (0.86 to 1.20)	1.00 (0.84 to 1.18)
WEEK 12:	0.82 (0.68 to 0.99)	0.95 (0.79 to 1.13)	0.83 (0.69 to 1.00)

P-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY		SECONDARY							
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.004	0.028	0.484	<0.001	0.001	0.712	0.285
WEEK 6:	<0.001*	<0.001*	<0.001	0.273	0.375	0.832	<0.001	0.358	0.859	0.973
WEEK 12:	<0.001*	<0.001*	<0.001	0.139	0.981	0.146	<0.001	0.036	0.541	0.039

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.825 for week 2, 0.941 for week 6, and 0.967 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

APPEARS THIS WAY ON ORIGINAL

Table A.9.1 Patient's Assessment of Arthritis Pain (protocol 020)

INTENT-TO-TREAT COHORT (ITT) *

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	201	203	196	201	197
MEAN	69.4	66.9	66.0	68.9	71.4
STD DEV	17.13	18.13	16.17	15.43	14.97
WEEK 2					
N	201	203	196	201	197
MEAN	56.1	49.2	41.9	44.0	42.2
STD DEV	26.24	25.53	25.77	24.96	26.52
WEEK 6					
N	201	203	196	201	197
MEAN	51.1	49.3	41.6	43.8	41.9
STD DEV	29.04	26.83	27.84	27.05	29.07
WEEK 12					
N	201	203	196	201	197
MEAN	52.7	50.9	43.8	45.5	45.8
STD DEV	29.41	28.29	28.05	29.23	29.29

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with lower score as better
* By definition, in this and subsequent efficacy tables, the ITT cohort includes only knee patients who had at least one dose of study medication

TABLE 18
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-13.3	-17.7	-26.1	-24.9	-29.2		
STD DEV	23.28	25.99	26.19	24.81	26.88		
LS MEAN CHANGE (c)	-12.1	-18.4	-26.1	-24.6	-27.3		
WEEK 6						<0.001	<0.001
OBSERVED MEAN CHANGE	-18.3	-17.7	-26.4	-25.1	-29.5		
STD DEV	27.38	29.22	27.76	26.40	30.28		
LS MEAN CHANGE (c)	-16.6	-17.9	-25.9	-24.5	-27.0		
WEEK 12						0.002	<0.001
OBSERVED MEAN CHANGE	-16.7	-16.0	-24.1	-23.3	-25.6		
STD DEV	29.05	29.81	27.31	29.18	29.14		
LS MEAN CHANGE (c)	-15.1	-16.0	-23.1	-22.1	-22.7		

Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):	50MG BID VS. NAPROXEN	100MG BID VS. NAPROXEN	200MG BID VS. NAPROXEN
WEEK 2:	0.67 (0.53 to 0.84)	0.96 (0.80 to 1.15)	0.90 (0.74 to 1.09)
WEEK 6:	0.66 (0.51 to 0.85)	0.96 (0.78 to 1.18)	0.91 (0.74 to 1.12)
WEEK 12:	0.70 (0.51 to 0.94)	1.02 (0.80 to 1.30)	0.97 (0.76 to 1.25)

p-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY		SECONDARY						
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG DID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	0.009	0.001	0.010	0.514	<0.001	<0.001	0.643	0.263
WEEK 6:	<0.001*	0.003*	0.628	0.002	0.013	0.579	<0.001	<0.001	0.700	0.346
WEEK 12:	0.003*	0.009*	0.735	0.008	0.023	0.701	0.005	0.014	0.875	0.822

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 23.93 for week 2, 26.22 for week 6, and 27.02 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table/Figure A.9.2 Patient's Assessment of Arthritis Pain (020)

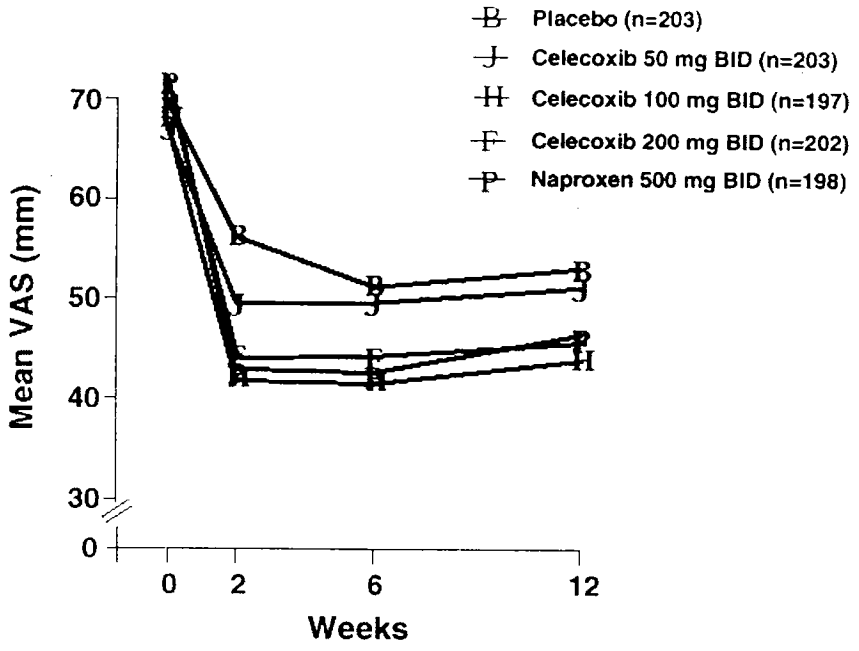

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Table A.10.1 Patient's Assessment of Arthritis Pain (protocol 054)

TABLE 18
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 1 OF 3: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	212	207
MEAN	68.0	64.	65.2	67.8	67.
STD DEV	14.49	16.16	16.99	15.69	16.43
WEEK 2					
N	217	216	207	213	207
MEAN	57.0	49.4	48.7	44.2	42.
STD DEV	24.66	25.93	26.09	27.11	25.14
WEEK 6					
N	217	216	207	213	207
MEAN	55.6	47.9	48.0	44.8	43.
STD DEV	26.11	28.15	27.93	29.65	27.11
WEEK 12					
N	217	216	207	213	207
MEAN	57.4	50.0	44.6	49.0	49.
STD DEV	25.71	28.69	29.13	28.89	27.10

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with lower score as better

TABLE 19
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO N=217	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-11.0	-18.3	-23.6	-23.6	-25.4		
STD DEV	24.62	24.87	25.40	25.48	24.95		
LS MEAN CHANGE (c)	-11.8	-19.7	-24.4	-24.4	-26.5		
WEEK 6						<0.001	<0.001
OBSERVED MEAN CHANGE	-12.6	-20.9	-24.2	-22.8	-23.6		
STD DEV	25.31	27.04	26.97	28.87	27.68		
LS MEAN CHANGE (c)	-13.2	-21.6	-25.1	-23.9	-24.8		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-10.8	-18.7	-22.6	-18.8	-21.4		
STD DEV	25.87	28.24	28.25	28.67	28.25		
LS MEAN CHANGE (c)	-11.1	-19.0	-23.3	-19.3	-22.3		

Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):	50MG BID VS. NAPROXEN	100MG BID VS. NAPROXEN	200MG BID VS. NAPROXEN
WEEK 2:	0.74 (0.61 to 0.91)	0.80 (0.76 to 1.10)	0.92 (0.79 to 1.08)
WEEK 6:	0.87 (0.69 to 1.08)	1.01 (0.82 to 1.24)	0.96 (0.79 to 1.16)
WEEK 12:	0.85 (0.68 to 1.10)	1.05 (0.83 to 1.32)	0.87 (0.69 to 1.10)

p-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY: 100MG BID VS. PLACEBO	PRIMARY: 200MG BID VS. PLACEBO	SECONDARY: 50MG BID VS. PLACEBO	SECONDARY: 100MG BID VS. 50MG BID	SECONDARY: 200MG BID VS. 100MG BID	SECONDARY: NAPROXEN VS. PLACEBO	SECONDARY: NAPROXEN VS. 50MG BID	SECONDARY: NAPROXEN VS. 100MG BID	SECONDARY: NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	<0.11	0.039	0.61	0.04*	<0.001	0.03	0.35
WEEK 6:	<0.001*	<0.001*	0.17	0.24	0.323	0.039	<0.001	0.179	0.57
WEEK 12:	<0.001*	0.011*	0.301	0.01	0.849	0.125	<0.001	0.179	0.479

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 mm with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and baseline value as covariate, the corresponding ROOT MSE was 24.29 for 2 weeks, 24.04 for 6 weeks and 24.78 for 12 weeks
(d) From a contrast statement for Analysis of Variance in which the treatment group was maximized
(e) Q-RATIO is defined as the ratio of least square mean changes from ... of Covariance with group means adjusted
(f) From a contrast statement in Analysis of Covariance model
* Statistically significant according to the primary (primary pairwise comparisons only)

Table/Figure A.10.2 Patient's Assessment of Arthritis Pain (054)

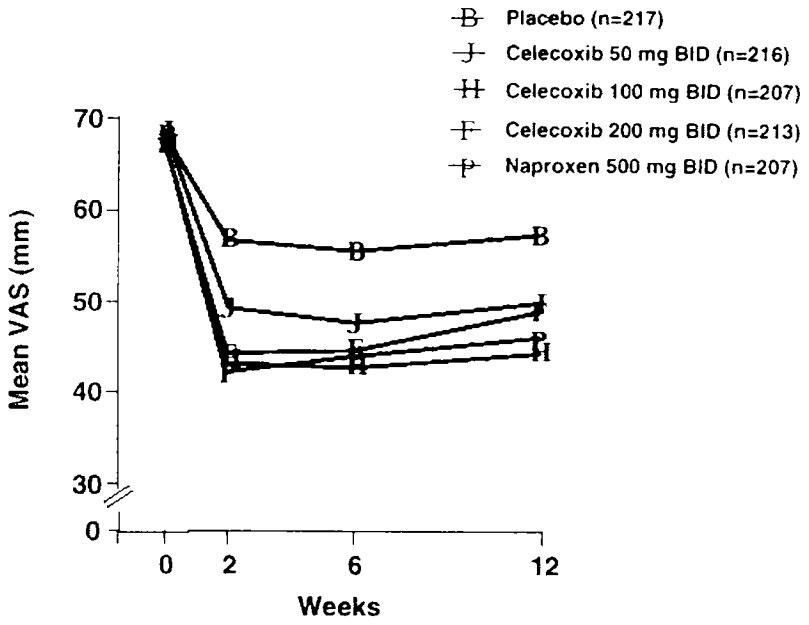

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Table A.11 WOMAC pain (protocol 054)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP OA
M49-96-02-054

TABLE 21.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	211	207
MEAN	10.6	10.5	10.6	10.8	10.5
STD DEV	3.25	3.4	3.33	2.95	3.54
WEEK 2					
N	217	216	207	212	207
MEAN	10.0	8.4	8.1	8.3	7.8
STD DEV	3.46	3.85	3.62	3.57	3.74
WEEK 12					
N	217	216	207	213	207
MEAN	9.7	8.0	8.5	8.5	8.0
STD DEV	3.98	3.99	4.22	4.20	3.94

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.6	-1.7	-2.5	-2.5	-2.7		
STD DEV	3.09	3.30	3.26	3.07	3.20		
LS MEAN CHANGE (c)	-0.7	-1.8	-2.6	-2.5	-2.9		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.9	-1.5	-2.1	-2.4	-2.5		
STD DEV	3.69	3.41	3.56	3.91	3.61		
LS MEAN CHANGE (c)	-1.0	-1.7	-2.6	-2.4	-2.7		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.004	0.009	0.804	<0.001	<0.001	0.394	0.271
WEEK 12:	<0.001	<0.001	0.034	0.093	0.028	0.607	<0.001	0.002	0.179	0.403

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

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Table A.12 WOMAC pain (protocol 020)

TABLE 21.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	201	197	196	201	198
MEAN	11.1	11.0	10.6	10.7	11.0
STD DEV	3.41	3.18	3.36	3.36	2.97
WEEK 2					
N	201	197	196	201	198
MEAN	10.0	8.7	7.6	7.9	8.2
STD DEV	3.99	3.77	3.79	3.80	4.00
WEEK 12					
N	201	197	196	201	198
MEAN	9.4	8.6	7.4	7.9	8.4
STD DEV	4.40	4.09	4.17	4.19	4.25

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

INTENT-TO-TREAT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(c)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.8	-2.0	-3.0	-2.8	-2.8		
STD DEV	2.98	3.16	3.29	3.58	3.85		
LS MEAN CHANGE (c)	-0.7	-2.0	-3.1	-2.8	-2.7		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-1.4	-2.1	-3.1	-2.8	-2.6		
STD DEV	3.84	3.99	3.66	3.84	3.91		
LS MEAN CHANGE (c)	-1.2	-2.0	-3.1	-2.7	-2.4		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.001	0.010	0.520	<0.001	0.024	0.340	0.751
WEEK 12:	<0.001	<0.001	0.026	0.002	0.049	0.259	0.001	0.310	0.038	0.339

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

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BEST POSSIBLE

Table A.13 WOMAC stiffness (protocol 054)

TABLE 21.2
WOMAC JOINT STIFFNESS
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	211	205
MEAN	4.6	4.7	4.6	4.7	4.6
STD DEV	1.42	1.48	1.54	1.40	1.60
WEEK 2					
N	217	216	207	212	207
MEAN	4.4	4.0	3.7	3.7	3.6
STD DEV	1.49	1.57	1.60	1.62	1.63
WEEK 12					
N	217	216	207	213	207
MEAN	4.3	3.9	3.7	3.7	3.6
STD DEV	1.59	1.61	1.77	1.66	1.64

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with lower score as better

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.3	-0.8	-1.0	-1.0	-1.0		
STD DEV	1.37	1.45	1.59	1.56	1.54		
LS MEAN CHANGE (c)	-0.3	-0.8	-1.0	-1.0	-1.1		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.3	-0.8	-0.9	-1.0	-1.0		
STD DEV	1.61	1.50	1.67	1.75	1.56		
LS MEAN CHANGE (c)	-0.4	-0.8	-1.0	-1.0	-1.1		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.046	0.031	0.895	<0.001	0.007	0.498	0.564
WEEK 12:	<0.001	<0.001	0.004	0.148	0.132	0.959	<0.001	0.017	0.354	0.379

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

APPEARS THIS WAY ON ORIGINAL

Table A.14 WOMAC stiffness (protocol 020)

TABLE 21.2
WOMAC JOINT STIFFNESS
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	202	197	196	201	195
MEAN	4.9	4.6	4.7	4.9	5.0
STD DEV	1.45	1.31	1.47	1.50	1.40
WEEK 2					
N	202	197	196	201	195
MEAN	4.4	3.9	3.6	3.6	3.7
STD DEV	1.59	1.54	1.65	1.62	1.69
WEEK 12					
N	202	197	196	201	195
MEAN	4.3	3.9	3.5	3.7	3.7
STD DEV	1.72	1.73	1.71	1.69	1.81

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with lower score as better

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.4	-0.9	-1.2	-1.3	-1.3		
STD DEV	1.33	1.49	1.58	1.66	1.93		
LS MEAN CHANGE (e)	-0.3	-0.9	-1.2	-1.2	-1.1		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.2	-1.2	-1.2		
STD DEV	1.61	1.60	1.57	1.71	1.90		
LS MEAN CHANGE (e)	-0.5	-0.9	-1.2	-1.1	-1.1		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.019	0.027	0.634	<0.001	0.091	0.510	0.613
WEEK 12:	<0.001	<0.001	0.013	0.026	0.149	0.449	<0.001	0.154	0.446	0.995

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.15 WOMAC function (protocol 054)

TABLE 71.3
WOMAC PHYSICAL FUNCTIONING
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	215	207	211	207
MEAN	35.5	34.1	34.9	35.4	34.7
STD DEV	11.30	12.09	12.24	11.13	12.31
WEEK 2					
N	217	215	207	212	207
MEAN	33.3	29.2	27.2	27.6	26.5
STD DEV	12.60	12.73	12.32	12.71	12.43
WEEK 12					
N	217	215	207	213	207
MEAN	33.5	29.3	26.2	26.2	26.8
STD DEV	12.90	13.64	14.75	13.79	13.20

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with lower score as better

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-2.2	-4.9	-7.7	-7.8	-8.2		
STD DEV	9.28	10.36	10.11	10.72	9.96		
LS MEAN CHANGE (c)	-2.3	-5.4	-8.0	-8.1	-8.9		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-3.0	-4.8	-6.7	-7.3	-7.9		
STD DEV	10.94	10.91	11.17	12.08	11.24		
LS MEAN CHANGE (c)	-3.2	-5.5	-7.0	-7.5	-8.4		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.101	0.005	0.004	0.945	<0.001	<0.001	0.470	0.511
WEEK 12:	<0.001	<0.001	0.023	0.142	0.047	0.609	<0.001	0.004	0.160	0.369

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.16 WOMAC function (protocol 020)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	164	174	176	181	180
MEAN	36.0	36.2	35.4	35.3	36.6
STD DEV	10.83	10.76	11.77	12.29	10.58
WEEK 6					
N	164	174	176	181	180
MEAN	33.0	29.3	26.2	26.9	28.1
STD DEV	12.52	13.06	12.88	12.94	13.23
WEEK 12					
N	164	174	176	181	180
MEAN	31.7	29.4	26.1	27.4	28.5
STD DEV	13.94	14.09	14.38	14.20	14.62

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with lower score as better

TABLE 21.3
WOMAC PHYSICAL FUNCTIONING
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=202)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-2.9	-6.9	-9.1	-8.4	-8.5		
STD DEV	9.32	9.85	11.19	11.38	12.53		
LS MEAN CHANGE (c)	-2.6	-6.8	-9.3	-8.5	-8.3		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-4.3	-6.8	-9.2	-7.9	-8.1		
STD DEV	11.21	11.61	12.26	12.62	13.23		
LS MEAN CHANGE (c)	-3.9	-6.8	-9.5	-8.1	-7.8		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.021	0.113	0.460	<0.001	0.257	0.233	0.647
WEEK 12:	<0.001	<0.001	0.018	0.033	0.301	0.265	0.001	0.438	0.170	0.794

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.17 WOMAC composite (protocol 054)

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	211	205
MEAN	50.7	49.3	50.2	50.9	49.5
STD DEV	14.98	15.07	16.06	14.33	16.65
WEEK 2					
N	217	216	207	212	207
MEAN	47.9	47.0	49.0	49.6	47.4
STD DEV	16.95	17.40	17.80	17.09	16.98
WEEK 12					
N	217	215	207	213	207
MEAN	46.5	42.2	40.4	40.3	38.4
STD DEV	17.68	18.66	19.99	18.92	17.97

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with lower score as better

WOMAC COMPOSITE SCORE
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-3.1	-7.3	-11.2	-11.4	-12.0		
STD DEV	10.59	13.99	13.91	14.22	13.74		
LS MEAN CHANGE (c)	-3.4	-8.0	-11.7	-11.7	-12.7		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-4.2	-7.2	-9.7	-10.6	-11.5		
STD DEV	15.07	14.73	15.28	16.83	15.43		
LS MEAN CHANGE (c)	-4.6	-8.0	-10.3	-11.0	-12.4		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.003	0.003	0.985	<0.001	<0.001	0.393	0.402
WEEK 12:	<0.001	<0.001	0.014	0.119	0.038	0.613	<0.001	0.002	0.138	0.126

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.18 WOMAC composite (protocol 020)

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT GROUP (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID N=203	SC-58635 100MG BID N=197	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	192	174	195	181	177
MEAN	51.6	51.8	50.5	51.0	52.9
STD DEV	14.80	14.39	15.67	16.36	13.97
WEEK 2					
N	162	174	195	181	177
MEAN	47.5	42.1	43.4	38.5	40.2
STD DEV	17.34	17.68	17.46	17.69	18.50
WEEK 12					
N	182	174	195	181	177
MEAN	45.5	42.3	37.2	39.0	41.0
STD DEV	19.32	19.29	19.46	19.31	20.69

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with lower score as better

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT GROUP (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2						<0.001	<0.001
OBSERVED MEAN CHANGE	-4.1	-9.7	-13.1	-12.5	-12.7		
STD DEV	12.55	13.52	14.82	15.76	17.19		
LS MEAN CHANGE (c)	-3.6	-9.7	-13.4	-12.5	-11.9		
WEEK 12						<0.001	<0.001
OBSERVED MEAN CHANGE	-6.1	-9.5	-13.3	-12.0	-11.9		
STD DEV	15.58	15.76	16.40	17.45	18.19		
LS MEAN CHANGE (c)	-5.6	-9.6	-13.6	-12.1	-11.8		

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.016	0.052	0.549	<0.001	0.137	0.296	0.650
WEEK 12:	<0.001	<0.001	0.016	0.019	0.144	0.154	<0.001	0.315	0.173	0.655

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.19 Withdrawal due to lack of Arthritis Efficacy (020, 054)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN OA
M49-96-02-020

TABLE 22
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	79(39%)	61(30%)	40(20%)	49(24%)	52(26%)

p-VALUES FOR OVERALL COMPARISONS (a): <0.001

p-VALUE FOR LINEAR TREND TEST (b): <0.001

p-VALUES FOR TREATMENT COMPARISONS (c):

50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.076	<0.001	0.002	0.029	0.219	0.400	0.008	0.438	0.190	0.647

(a) Fisher's Exact test for all five treatment groups
(b) Cochran-Mantel-Haenszel test of linear dose trend (Nonzero Correlation), Naproxen group was excluded
(c) Pairwise Fisher's Exact test

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP OA
N49-96-02-054

TABLE 22
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	112(52%)	76(35%)	61(29%)	55(26%)	51(25%)

p-VALUES FOR OVERALL COMPARISONS (a): <0.001

p-VALUE FOR LINEAR TREND TEST (b): <0.001

p-VALUES FOR TREATMENT COMPARISONS (c):

50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
<0.001	<0.001	<0.001	0.214	0.037	0.445	<0.001	0.020	0.319	0.616

(a) Fisher's Exact test for all five treatment groups
(b) Cochran-Mantel-Haenszel test of linear dose trend (Nonzero Correlation), Naproxen group was excluded
(c) Pairwise Fisher's Exact test

Table A.20 Time to Withdrawal-Lack of Arthritis Efficacy (054)

TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS
WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY
INTENT-TO-TREAT COHORT (ITT)

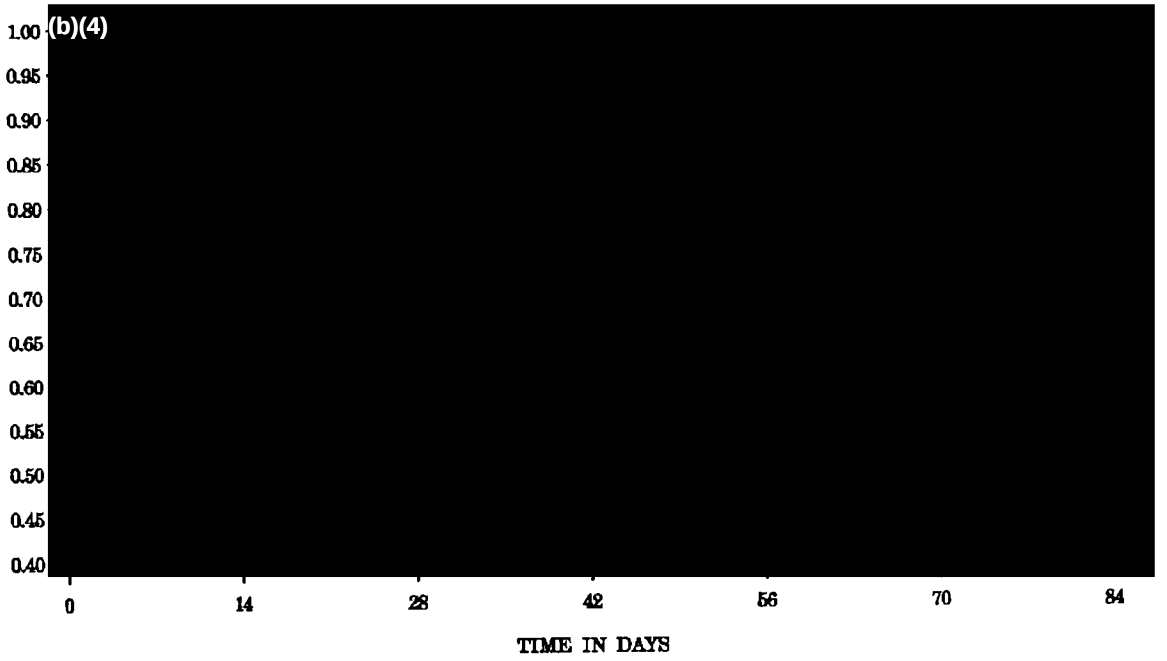


TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

p-VALUE FOR OVERALL COMPARISONS (a): <0.001

p-VALUES FOR TREATMENT COMPARISONS (b):

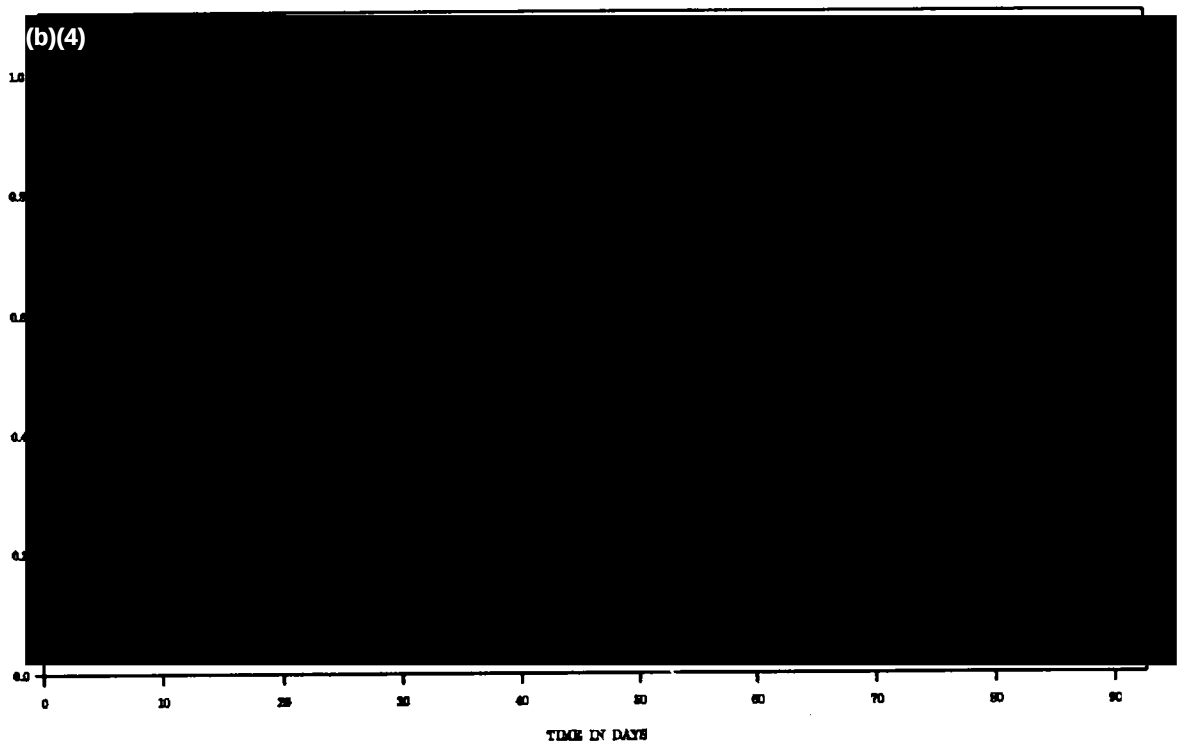
50MG BID vs. PLACEBO	100MG BID vs. PLACEBO	200MG BID vs. PLACEBO	100MG BID vs. 50MG BID	200MG BID vs. 50MG BID	200MG BID vs. 100MG BID	NAPROXEN vs. PLACEBO	NAPROXEN vs. 50MG BID	NAPROXEN vs. 100MG BID	NAPROXEN vs. 200MG BID
<0.001	<0.001	<0.001	0.155	0.046	0.544	<0.001	0.024	0.569	1.772

(a) From log rank test for all five treatment groups
(b) From pairwise treatment test

Table A.21 Time to Withdrawal-Lack of Arthritis Efficacy (020)

TABLE 22
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)



SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN OA
M49-96-02-020

TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

p-VALUE FOR OVERALL COMPARISONS (a): <0.001

p-VALUES FOR TREATMENT COMPARISONS (b):

50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.017	<0.001	<0.001	0.065	0.142	0.648	0.002	0.420	0.295	0.530

(a) From log-rank test for all five treatment groups
(b) From pairwise log-rank test

Table A.22.1 Reasons for Study Termination (020, 021, 054)

Study	Number of Osteoarthritis Patients by Treatment Group				
		Celecoxib			Naproxen
	Placebo	50 mg BID	100 mg BID	200 mg BID	500 mg BID
Study 020[a]	**(n=204[b])**	**(n=203)**	**(n=197)**	**(n=202)**	**(n=198)**
Total Completed	**91 (45%)**	**118 (58%)**	**116 (59%)**	**129 (64%)**	**116 (59%)**
Total Withdrawn	**113[b] (55%)**	**85 (42%)**	**81 (41%)**	**73 (36%)**	**82 (41%)**
Lost to Follow-up	3 (1%)	1 (<1%)	3 (2%)	1 (<1%)	3 (2%)
Pre-Existing Violation	3 (1%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Protocol Non-Compliance	12 (6%)	4 (2%)	7 (4%)	2 (<1%)	8 (4%)
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 (9%)
Study 021[a]	**(n=242)**	**(n=252)**	**(n=240[b])**	**(n=233)**	**(n=226)**
Total Completed	**119 (49%)**	**168 (67%)**	**165 (69%)**	**154 (66%)**	**147 (65%)**
Total Withdrawn	**123 (51%)**	**84 (33%)**	**75[b] (31%)**	**79 (34%)**	**79 (35%)**
Lost to Follow-up	5 (2%)	1 (<1%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Protocol Non-Compliance	13 (5%)	8 (3%)	7 (3%)	4 (2%)	8 (4%)
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 (6%)	16 (6%)	16 (7%)	23 (10%)	30 (13%)
Study 054	**(n=218[b])**	**(n=216)**	**(n=207)**	**(n=213)**	**(n=207)**
Total Completed	**79 (36%)**	**111 (51%)**	**111 (54%)**	**119 (56%)**	**118 (57%)**
Total Withdrawn	**139[b] (64%)**	**105 (49%)**	**96 (46%)**	**94 (44%)**	**89 (43%)**
Lost to Follow-up	2 (<1%)	4 (2%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Protocol Non-Compliance	5 (2%)	6 (3%)	8 (4%)	9 (4%)	7 (3%)
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 (7%)	17 (8%)	27 (13%)	25 (12%)	29 (14%)
Pooled 12-Week Pivotal Studies	**(n=664[b])**	**(n=671)**	**(n=644[b])**	**(n=648)**	**(n=631)**
Total Completed	**289 (44%)**	**397 (59%)**	**392 (61%)**	**402 (62%)**	**381 (60%)**
Total Withdrawn	**375[b] (56%)**	**274 (41%)**	**252[b] (39%)**	**246 (38%)**	**250 (40%)**
Lost to Follow-up	10 (2%)	6 (2%)	3 (<1%)	5 (<1%)	5 (<1%)
Pre-Existing Violation	8 (1%)	6 (2%)	1 (<1%)	4 (<1%)	2 (<1%)
Protocol Non-Compliance	30 (4%)	18 (6%)	22 (3%)	15 (2%)	23 (4%)
Treatment Failure	284 (42%)	193 (29%)	152 (24%)	153 (24%)	143 (23%)
Adverse Event	46 (7%)	51 (8%)	74 (11%)	69 (11%)	77 (12%)

Derived from Individual Study Reports

a) Includes only patients with OA of the knee.

b) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]), who were randomized into a study but did not receive study medication and are not included in the ITT Cohort.

Table A.22.2 Reasons for Study Termination (060, 087)

	Number of Osteoarthritis Patients by Treatment Group		
		Celecoxib	
Study	Placebo	100 mg BID	200 mg QD
Study 060	**(n=232)**	**(n=231)**	**(n=223)**
Total Completed	**146 (63%)**	**194 (84%)**	**182 (82%)**
Total Withdrawn	**86 (37%)**	**37 (16%)**	**41 (18%)**
Lost to Follow-up	2 (<1%)	4 (2%)	2 (<1%)
Pre-Existing Violation	2 (<1%)	2 (<1%)	2 (<1%)
Protocol Non-Compliance	6 (3%)	2 (<1%)	7 (3%)
Treatment Failure	56 (24%)	18 (8%)	21 (9%)
Adverse Event	20 (9%)	11 (5%)	9 (4%)
Study 087	**(n=244)**	**(n=243)**	**(n=231)**
Total Completed	**164 (67%)**	**194 (80%)**	**191 (83%)**
Total Withdrawn	**80 (33%)**	**49 (20%)**	**40 (17%)**
Lost to Follow-up	1 (<1%)	0 (0%)	1 (<1%)
Pre-Existing Violation	4 (2%)	6 (2%)	4 (2%)
Protocol Non-Compliance	8 (3%)	7 (3%)	5 (2%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 (5%)	9 (4%)	6 (3%)
Pooled 6-Week Pivotal Studies	**(n=476)**	**(n=474)**	**(n=454)**
Total Completed	**310 (65%)**	**388 (82%)**	**373 (82%)**
Total Withdrawn	**166 (35%)**	**86 (18%)**	**81 (18%)**
Lost to Follow-up	3 (1%)	4 (1%)	3 (1%)
Pre-Existing Violation	6 (1%)	8 (2%)	6 (1%)
Protocol Non-Compliance	14 (3%)	9 (2%)	12 (3%)
Treatment Failure	111 (23%)	45 (9%)	45 (10%)
Adverse Event	32 (7%)	20 (4%)	15 (3%)

Derived from Individual Study Reports

Table A.23 Schedule of Observations and Procedures (Protocol 060)

	Pretreatment Period		Treatment Period		
	Screening Visit (-14 to-2 days)	Baseline Visit (Day 0)	Week 2 (Day 14) (±2 days)	Week 6 (Day 42) (±4 days)	Early Termination
Informed Consent	x				
Medical History	x				
Physical Exam	x			x	x
Clinical Lab Tests[a]	x		x	x	x
SF-36 Health Survey		x		x	x
OA Assessments[b]	x[c]	x	x	x	x
Discontinued NSAID or Analgesic[d]	x				
Meet Flare Criteria		x			
Signs & Symptoms		x	x	x	x
Dispense Study Med		x	x		
Return & Count Study Med			x	x	x
Dispense Con Med Diary Card		x	x		
Retrieve Con Med Diary Card			x	x	x
Blood Sample For PK[e]			x	x	

(a) Clinical laboratory tests included: **Hematology** (white blood cell [WBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable]) and **Biochemistry** (BUN, creatinine, total bilirubin, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]). **Urinalysis** (pH, specific gravity, WBC, red blood cell [RBC], protein, glucose, ketones, bilirubin) at Screening Visit only. Serum pregnancy test for women of childbearing potential at Screening Visit only.

(b) Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Pain - Visual Analog Scale (VAS), Physician's Global Assessment of Arthritic Condition, Functional Capacity Classification, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Osteoarthritis Severity Index.

(c) Screening arthritis assessment data was not collected by Searle. Patient's Assessment of Pain (VAS) and WOMAC were not performed at the Screening Visit.

(d) Patient discontinued NSAID or analgesic use within 48 hours or at least five half-lives before the Baseline Arthritis Assessments, whichever was greater.

(e) Blood samples were collected at selected investigational sites only.

Table A.24.1 Patient's global assessment (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
M49 96 CD 087

TABLE 15
PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT TO TREAT COHORT (ITT) *

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)
BASELINE			
N	243	241	231
MEAN	3.4	3.5	3.4
STD DEV	0.60	0.58	0.60
WEEK 2			
N	243	241	231
MEAN	3.0	2.7	2.7
STD DEV	0.90	0.90	0.85
WEEK 6			
N	243	241	231
MEAN	3.0	2.8	2.6
STD DEV	1.02	0.99	0.95

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor)
* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)	p VALUE (a)
WEEK 2				<0.001
IMPROVED (b)	56(23%)	99(41%)	71(31%)	
NO CHANGE	176(72%)	137(57%)	160(69%)	
WORSENED (c)	11(5%)	5(2%)	0(0%)	
TOTAL	243(100%)	241(100%)	231(100%)	
WEEK 6				0.004
IMPROVED (b)	65(27%)	90(37%)	87(38%)	
NO CHANGE	160(66%)	143(59%)	143(62%)	
WORSENED (c)	16(7%)	8(3%)	1(<1%)	
TOTAL	241(100%)	241(100%)	231(100%)	

p VALUES FOR TREATMENT COMPARISONS (d) :

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	0.009	0.107
WEEK 6:	0.020	0.001	0.479

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from Baseline for grades 3 5 or a change in grade from 2 to 1
(c) Worsened is defined as an increase of at least two grades from Baseline for grade 1 3 or a change in grade from 4 to 5
(d) Cochran-Mantel-Haenszel test stratified by Wscat (Raw Mean Pooled Pilot)

BEST POSSIBLE

Table A.24.2 Patient's Global Assessment (Protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
M49-98-02-087

TABLE 15
PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 3 OF 4: MEAN CHANGE ANALYSIS (A) (B)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=243)	SC-58635 100MG BID (N=241)	SC-58635 200MG QD (N=231)	P-VALUE(C)
WEEK 2				<0.001
OBSERVED MEAN CHANGE	0.6	-1.2	-1.1	
STD DEV	0.99	0.99	0.94	
LS MEAN CHANGE (C)	-0.8	-1.1	-1.1	
WEEK 6				<0.001
OBSERVED MEAN CHANGE	-0.8	-1.1	-1.2	
STD DEV	1.10	1.06	1.05	
LS MEAN CHANGE (C)	0.8	-1.1	-1.2	

Q-RATIO WITH 95% CONFIDENCE INTERVALS (D): 200MG QD VS. 100MG BID

WEEK 2:	1.00 (0.86 to 1.15)
WEEK 6:	1.03 (0.96 to 1.10)

p-VALUES FOR TREATMENT COMPARISONS (E):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	<0.001	0.963
WEEK 6:	0.008	<0.001	0.156

(a) This table is based on the last observation carried forward approach.
(b) Pain ranges from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
the corresponding MSAT MSE are: 0.647 for week 2, and 0.973 for week 6
(d) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 200MG QD versus SC-58635 100MG BID
(e) From a contrast statement from Analysis of Covariance model in (c)

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Table A.25.1 Physician's Global Assessment (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49 98 02 087

TABLE 17
PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT TO TREAT COHORT (ITT)

	PLACEBO	SC-58635 100MG BID	SC-58635 200MG QD
	(N 243)	(N 241)	(N 231)
BASELINE			
N	243	240	231
MEAN	3.8	3.8	3.7
STD DEV	0.67	0.61	0.65
WEEK 2			
N	243	241	231
MEAN	3.0	2.8	2.7
STD DEV	0.83	0.84	0.79
WEEK 6			
N	243	241	231
MEAN	3.0	2.7	2.6
STD DEV	0.95	0.91	0.89

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor)

	PLACEBO	SC-58635 100MG BID	SC-58635 200MG QD	p VALUE (d)
	(N 243)	(N 241)	(N 231)	
WEEK 2				<0.001
IMPROVED (b)	47(19%)	93(39%)	66(29%)	
NO CHANGE	186(77%)	144(60%)	164(71%)	
WORSENED (c)	6(3%)	3(1%)	1(<1%)	
TOTAL	243(100%)	240(100%)	231(100%)	
WEEK 6				0.012
IMPROVED (b)	59(24%)	84(35%)	80(35%)	
NO CHANGE	172(71%)	151(63%)	151(65%)	
WORSENED (c)	12(5%)	5(2%)	0(0%)	
TOTAL	243(100%)	240(100%)	231(100%)	

p VALUES FOR TREATMENT COMPARISONS (d)

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	0.008	0.031
WEEK 6:	0.022	0.004	0.813

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from Baseline for grades 2 5 or a change in grade from 2 to
(c) Worsened is defined as an increase of at least two grades from Baseline for grades 1-3 or a change in grade from 4 to 5
(d) Cochran-Mantel-Haenszel test stratified by region (Row Mean Scores Differ)

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BEST POSSIBLE

Table A.25.2 Physician's Global Assessment (protocol 087)

SC-56468 ID VS BID EFFICACY IN RHEE DA
[illegible]

TABLE 17
PHYSICIAN'S GLOBAL ASSESSMENT OF PATIENTS
(PART 2 OF 4: MEAN PAUSE ANALYSIS [illegible])

[illegible] MEAN [illegible]

	PLACEBO (N 243)	SC-56468 100MG BID (N 241)	SC-56468 200MG QD (N 231)	p VALUE [illegible]
WEEK 2				<0.001
OBSERVED MEAN CHANGE	0.8	1.2	1.1	
STD DEV	0.90	0.87	0.88	
LS MEAN CHANGE (c)	-0.7	-1.1	-1.1	
WEEK 6				<0.001
OBSERVED MEAN CHANGE	-0.8	-1.1	-1.2	
STD DEV	1.01	0.96	1.01	
LS MEAN CHANGE (c)	0.8	1.2	1.2	

Q-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID

WEEK 2:	0.90	(0.84 to 1.10)
WEEK 6:	1.10	(0.97 to 1.32)

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	<0.001	0.553
WEEK 6:	0.003	<0.001	0.105

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.746 for week 2, and 0.693 for week 6
(d) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-56468 200MG QD versus SC-56468 100MG BID
(e) From a contrast statement from Analysis of Covariance model in (c)

APPEARS THIS WAY ON ORIGINAL

Table A.26 Patient's Assessment of Arthritis Pain (protocol 060)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=231)	SC-58635 200MG QD (N=222)
BASELINE			
N	231	231	222
MEAN	68.1	67.8	68.0
STD DEV	15.16	16.52	16.74
WEEK 2			
N	231	231	222
MEAN	55.5	42.7	42.0
STD DEV	24.65	24.59	23.75
WEEK 6			
N	231	231	222
MEAN	54.0	40.3	41.0
STD DEV	26.00	28.01	26.29

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with lower score as better

SC-58635 QD VS BID EFFICACY IN KNEE OA
H49-96-02-060

TABLE 17
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=231)	SC-58635 200MG QD (N=222)	p-VALUE(c)
WEEK 2				<0.001
OBSERVED MEAN CHANGE	-12.6	-25.1	-25.9	
STD DEV	24.55	25.18	25.05	
LS MEAN CHANGE (c)	-12.9	-25.5	-26.1	
WEEK 6				<0.001
OBSERVED MEAN CHANGE	-14.1	-27.5	-26.9	
STD DEV	25.88	27.78	28.41	
LS MEAN CHANGE (c)	-14.8	-28.5	-27.7	

Q-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID

WEEK 2:	1.02 (0.85 to 1.23)
WEEK 6:	0.97 (0.81 to 1.17)

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	<0.001	0.780
WEEK 6:	<0.001	<0.001	0.747

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 23.37 for week 2, and 25.69 for week 6
(d) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 200MG QD versus SC-58635 100MG BID
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.27 Patient's Assessment of Arthritis Pain (protocol 087)

INTENT TO TREAT COHORT (ITT)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)
BASELINE			
N	243	241	231
MEAN	66.2	67.6	65.2
STD DEV	16.51	14.43	16.43
WEEK 2			
N	243	241	231
MEAN	54.1	45.5	44.4
STD DEV	25.33	24.19	23.90
WEEK 6			
N	243	241	231
MEAN	50.3	45.6	42.8
STD DEV	27.09	27.63	26.54

(a) This table is based on the last observation carried forward approach
(b) Scale ranges from 0 to 100 (mm with lower scores as better)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-98-02 087

TABLE 16
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT TO TREAT COHORT (ITT)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)	P VALUE(c)
WEEK 2				<0.001
OBSERVED MEAN CHANGE	-14.1	-24.1	-20.8	
STD DEV	24.75	26.35	24.44	
LS MEAN CHANGE (c)	-19.4	-22.5	-21.3	
WEEK 6				0.157
OBSERVED MEAN CHANGE	-15.8	-22.8	-22.5	
STD DEV	27.34	28.92	28.74	
LS MEAN CHANGE (c)	15.9	-21.2	23.9	

D-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID

WEEK 2:	0.84 (0.76 to 1.25)
WEEK 6:	1.11 (0.88 to 1.40)

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	<0.001	0.520
WEEK 6:	0.011	<0.001	0.344

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and baseline value as covariate.
the corresponding adjusted SDs are 19.40 for week 2, and 20.46 for week 6
(d) D-RATIO is defined as the ratio of least squared mean changes from (c), of SC-58635 200MG QD versus SC-58635 100MG BID
(e) From a contrast statement from Analysis of Covariance model in (c).

BEST POSSIBLE

Table A.28 WOMAC pain (protocol 060)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-MK-02-CRC

TABLE 11.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO	SC-58635 100MG BID	SC-58635 200MG QD
	(N=231)	(N=231)	(N=222)
BASELINE			
N	231	231	220
MEAN	10.5	10.6	10.8
STD DEV	3.48	3.40	3.68
WEEK 6			
N	231	230	220
MEAN	6.9	7.3	7.5
STD DEV	4.00	3.99	4.14

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO	SC-58635 100MG BID	SC-58635 200MG QD	p-VALUE (c)
	(N=231)	(N=231)	(N=222)	
WEEK 6				<0.001
OBSERVED MEAN CHANGE	-1.4	-3.0	-2.7	
STD DEV	3.63	3.52	3.91	
LS MEAN CHANGE (c)	1.5	3.1	2.9	

p-VALUES FOR TREATMENT COMPARISONS (d):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 6:	<0.001	<0.001	0.473

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline Value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c)

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Table A.29 WOMAC pain (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N43 96 02 087

TABLE 29.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT TO TREAT COHORT (ITT)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)
BASELINE			
N	239	239	229
MEAN	10.5	10.1	10.1
STD DEV	3.38	3.48	3.52
WEEK 6			
N	240	240	231
MEAN	6.7	7.4	7.1
STD DEV	4.11	4.47	4.08

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

INTENT TO TREAT COHORT (ITT)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)	p VALUE (c)
WEEK 6				<0.001
OBSERVED MEAN CHANGE	1.8	2.6	3.0	
STD DEV	4.07	4.52	4.57	
LS MEAN CHANGE (d)	-1.6	-2.6	-3.0	

p-VALUES FOR TREATMENT COMPARISONS (d):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 6:	0.005	<0.001	0.270

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c)